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C-REACTIVE PROTEIN TEST IN PATIENTS WITH FOCI OF CHRONIC ORAL INFECTIONS AND CIRCULATORY AND COLLAGEN DISEASES

[Following is the translation of an article by V.N. Latysh, Master of Medical Sciences, Faculty for Military-Field Therapy (Head - Prof. Ye. B. Zakrzhevskiy) of the Military-Medical Order of Lenin Academy imeni S. M. Kirova, Leningrad, published in the Russian-language periodical Terapevticheskiy Arkhiv (Therapeutic Archives), 37 (8), 1965, pages 82-88. It was submitted on 22 November 1964. Translation performed by Sp/7 Charles T. Ostertag, Jr.]

We undertook the mission of summing up the experience of many years on the study of the diagnostic value of CRP, based on diverse materials.

For the determination of CRP we used the semiquantitative method of microprecipitation in capillaries according to Anderson and McCarty, as modified by a number of authors (V.N. Latysh; P.M. Pashinin, et al). In evaluating the probes we were guided by the following criteria: Strongly positive test - with the height of the precipitate 4 mm and greater; positive - 3-2 mm; slightly positive - 1 mm and less ""traces"), and negative, when the precipitate was absent.

We investigated 972 persons, including 77 healthy persons (control), 92 with foci of chronic (oral) infection, 244 with circulatory diseases, and 559 with collagen diseases. The patients were present for treatment in hospital clinics and military-field therapy clinics since October 1958. In all of the patients upon admission, and in the majority of them dynamically (during treatment and before discharge) CRP was determined. All told 2314 tests were set up.

The clinical material and the results of tests for CRP in healthy persons and patients upon admission are presented in the table.

It can be seen from the table that CRP is apparent in a very moderate quantity during chronic periodontitis and in 34% of the cases during chronic tonsillitis. It was revealed in somewhat large concentrations in all four patients with chronic highmoritis. All of this testifies that in foci of chronic infection, frequently accompanying the main disease, conditions may be created for the formation of CRP.

Data on it during some diseases of the circulatory organs are interesting.

As it should have been expected, in all 23 patients with neurocirculatory dystonia (cardinal, hypo- and hypertensive types) CRP was absent in the blood.

Out of 82 patients with stenocardia it was not detected in 72, and the appearance of it in 10 men in insignificant quantities was connected with accompanying foci of chronic infection. At the same time CRP was exposed in quite significant quantities in all 87 patients with mycocardial infarction (the absence of CRP in 2 of those investigated was explained by the fact that the tests on them were set up in later periods from the day of development of the disease).

This indicates that the test for CRP may serve as an additional differential-diagnostic feature between stenocardia and myocardial infarction. CRP determination should be considered particularly valuable in cases of prolonged stenocardia, when changes in the ECG testify to ischemia of a sector of the myocardium, and at first these changes are difficult to distinguish from focal. The CRP test is of very great help in the diagnosis of multiple symmetrical injuries of the myocardium (as a rule, in such cases changes are revealed on the ECG) and recurrent infarcts, when against a background of old cicatricial changes the ECG is doubtful. Thus, we observed 4 patients in which the strongly positive CRP test helped to correctly diagnose recurrent myocardial infarction.

Dynamic observations show that during myocardial infarction CRP is apparent in the blood already by the end of the first to the beginning of the 2nd day, preceding an accelerated ESR, sometimes the development of leukocytosis, and sometimes even changes in the ECG. The more extensive the sector of myomalacia the greater the amount of precipitate; based on it, it was also possible to judge to a certain degree on the severity of the disease. During the first days a correlation is usually observed between the CRP content and an accelerated ESR (if a deficiency of circulation is not connected), the level of transmaminase and sialic acids, and also leukocytosis and changes in the ECG.

In patients with myocardial infarction of moderate severity CRP begins to disappear from the blood in the 2-4th week, often preceding the lowering of the ESR to the original figures and the normalization of the ECG. During extensive injury of the myocardium CRP may be detected in the blood in small quantities after 4-6 weeks and longer from the moment of development of the disease, indicating the processes of resorption and replacement of the necrotized sector of the myocardium with connective tissue. In individual cases the CRP test continued to come out positive for more than 3 months, in spite of the fact that the ESR and leukocytosis were normalized considerably earlier.

The detection of CRP for a prolonged period of time in patients with myocardial infarction compels the doctor to be very careful in respect to regimen and prognosis, since such findings may testify to a continuing or recurrent thrombosis. Along with this, repeated negative CRP tests and normalization of the generally applied laboratory and instrument tests (considering the clinical picture) serve as indications of the more or less

complete repair of the myocardium and may be an indication for expanding the patient's regimen.

It is essential to point out that during a simultaneous study of the leading clinical-laboratory and instrument indices in 67 patients with myocardial infarction (upon admission) CRP was revealed in 66, doubtless changes in the ECG - in 62, accelerated ESR - in 47, leukocytosis - in 45, and an increased body temperature - in 37 of those investigated.

Among 47 patients with protracted septic endocarditis CRP was detected in 41, primarily in moderate and less than moderate quantities. As a rule, in those patients in which the CRP test came out strongly positive, complications of the focal pneumonia type were diagnosed. A greater quantity of CRP precipitate corresponded to a more expressed clinical manifestation of the acuity of the inflammatory process during protracted septic endocarditis, which is usually reflected by fever. However, a correlation was not observed between the CRP and the ESR; CRP could be detected during a slowed down ESR and was absent or appeared in a neglible amount with a considerably speeded up ESR (the latter took place most often of all in cases, complicated by chronic diffuse glomerulonephritis).

Under the influence of antibiotic and hormone preparation treatment, in the majority of patients with protracted septic endocarditis along with clinical improvement there was noted a lowering in the level, and sometimes the disappearance, of CRP from the blood. It should be stressed that it could disappear from the blood, in spite of the fact that the ESR was lowered, and even if it continued to remain accelerated, and the formol reaction and the endothelial tests were positive. All of this indicates that the CRP, reflecting more profound changes during inflammation, is often reduced to quantities which are not discerned by the microprecipitation method, already during attenuation alone or the transition of subacute chroniosepsis into a latent course.

In comparing the frequency of detecting CRP and positive generally used laboratory tests we could not note an expressed diagnostic advantage of the CRP tests, though they could help in more reliably following the course of protracted septic endocarditis and the effectiveness of treatment (taking into consideration the clinical picture). Thus, out of 47 patients observed by us, the ESR was accelerated in 42, CRP was detected in 41, microhematuria - in 38, positive Waldman tests - in 34, positive formol reaction - in 31, monocytosis - in 23, positive Bittorf-Tushinskiy test - in 18, anemia - in 17, and leukopenia - in 14 persons.

During certain collagen diseases CRP presents a variegated picture.

In all 8 patients with erythematous chroniosepsis CRP was exposed in a moderate amount. During expressed clinical manifestations of the disease large quantities of it were usually determined. Under the influence of

hormone therapy CRP slowly disappeared from the blood along with the improved condition of the patient; when the dose was lowered or corticosteroids cancelled, CRP appeared rapidly in the blood again. The bond between the frequency of positive findings of LE-cells and the content of CRP in the blood was not established.

Among 134 patients with rheumatoid arthritis, who were investigated jointly with P. M. Pashinin, CRP was detected in 80% of them on admission. During the exudative stage of the disease, which is characterized by an acute and subacute course, it appeared in the blood in considerable quantities in all those investigated. Under the influence of complex therapy, if the process did not become chronic, CRP gradually disappeared from the blood after 3-6 weeks from the onset of the disease. In cases, proceeding subacutely, CRP could be detected in the blood for up to 6-8 months.

During the transition of rheumatoid arthritis into a fibrous stage, but with an expressed predominance of exudative symptoms during a period of aggravation, which was expressed clinically in a progressing (chronic) course of the illness with frequent relapses against a background of gradually developing contractures, deformations and ankyloses of the joints, CRP in smaller quantities was revealed in 70% of the cases. In spite of active treatment, the CRP in such patients, though distinctly lowered, continued to be determined in the blood for a long time, rarely disappeared during the period of short-term remissions, and during relapses appeared again in significant amounts in practically 100% of the patients.

During a settled fibrous stage of rheumatoid arthritis without an inclination to aggravation, CRP was detected in small concentrations in half of those investigated, regardless of the developed irreversible deformations of the joints, ankyloses, contractures and deformations of osseous tissue. As a rule, during the period of rare relapses the CRP test came out positive.

In comparison with the positive generally used laboratory tests, CRP was detected more often in patients with rheumatoid arthritis. Thus, if the CRP test came out positive in 80%, then the ESR turned out to be accelerated in 72%, and leukocytosis was established in only 67% of the cases.

In the 416 patients with rheumatism the active phase of the disease was noted in 306, and the nonactive - in 110. The clinical picture in 47 of the patients with rheumatism in the active phase was established by changes in the joints, and in 258 - by injury to the valvular apparatus and the myocardium. An acute and subacute course of the process was observed in 79, and a relapsing or flaccid (latent) course - in 227 of those investigated. Circulatory deficiency of the O-I degree was revealed in 130, IIA degree - in 76, IIB degree - in 79, and III degree - in 21

persons. In 148 patients with rheumatism a diagnosis was made of foci of chronic infection (tonsillitis, highmoritis, adnexitis, etc.).

A study of the data summarized in the table shows that during the initial determination CRP was detected in 81% of the cases in patients with rheumatism in the active phase. The acute and subacute course of the rheumatic process was accompanied by the appearance of CRP in all those investigated, usually in a significant amount. A conformity was observed between the expressiveness of clinical manifestations, temperature and the ESR on the one hand, and the level of CRP in the blood on the other. At the same time we established the dependency of the content of CRP on the day the patient was examined; the longer the period of time from the day the attack developed, the smaller the amount of precipitate. During relapsing and especially flaccid (latent) courses of rheumatism CRP was exposed primarily in moderate concentrations in 76% of the cases without a noticable correlation with temperature, period of investigation, etc.

Attention is merited by the dynamic observations of the CRP content.

During the joint-cardiac form of rheumatism, usually proceeding acutely and subacutely, CRP in a significant amount appeared in the blood regardless of heart injury in practically all those investigated. An exception were patients with erythema nodosum, in which it was detected in the presence of polyarthritis or rheumatic carditis. Under the influence of treatment the CRP level was reduced rapidly, in somewhat the same manner as the ESR was slowed down. Then the CRP disappeared from the blood, though the ESR became normal later. It should be stressed that the prolonged presence of CRP in small concentrations in patients with the joint-cardiac form of rheumatism after the liquidation of joint manifestations testified to the transition of the process into a relapsing course and to endomyocarditis (taking into consideration the clinical picture).

During the cardiac form of rheumatism, characterized by a residual, less often flaccid (latent), and even less often subacute, course, CRP was detected primarily in a moderate amount in 78% of the cases. The CRP tests proved to be a great help in exposing activity primarily in patients with a flaccid course of the rheumatic process on a background of lengthy treatment or formed heart defects and with an expressed circulatory deficiency, when the clinical symptoms are not clear and the ESR often is not speeded up.

Thus, while with a circulatory deficiency of the 0-I degree CRP was detected just as frequently as with an accelerated ESR, with a circulatory deficiency of the IIA degree it was determined 1.4 times more often, with the IIB degree - 2.5 times more often, and with the III degree - 2.8 times more often than was the accelerated ESR. However, in patients with "old" heart defects, complicated by circulatory deficiency of the III degree, often there were quite large concentrations of CRP, though clinical data, testifying to an acute course of the disease, were not noted. We connected

this not so much with the activity of the process as with the destructive changes in the internal organs (especially in the liver). In patients with a flaccid course of illness CRP could be detected in a small quantity for months, sometimes disappearing from the blood and thereby creating an impression of the onset of clinical remission. As a rule, when treatment was abolished it appeared again.

Under the influence of antirheumatic treatment of patients in the active phase of the disease a lowering of the level and the disappearance of CRP from the blood took place. If on admission, among 227 patients in which the test was studied dynamically it was detected in 84%, and during the process of observation even in 95%, then with the attenuation of the activity of the process and the onset of clinical remission (before discharge), CRP was revealed in small quantities in 46% of the cases. Of the 110 patients with rheumatism in the non-active phase it was determined primarily in the form of "traces" in 14% of those investigated. It should be stressed that the appearance of CRP in 1/8 of the patients with rheumatism in the active phase prior to discharge and in all the patients in the non-active phase of the disease is connected with the presence of foci or chronic infection.

Does the disappearance of CRP testify to the liquidation of the activity of the process? Our observations show that with the onset of clinical remission CRP is usually lacking in the blood. However, in a number of cases (especially against a background of intensive hormone therapy) it may disappear from the blood in spite of the fact that certain symptoms and generally accepted laboratory tests point to a current rheumatic process. Therefore, we consider clinical remission as achieved only when the CRP is not detected repeatedly after abolition of antirheumatic therapy, the ESR is not speeded up, the amount of leukocytes is normal, and the endothelial tests are negative. Along with this, the appearance of an insignificant amount of CRP in rheumatism patients when foci of chronic infection are present, if the other indices are normal, does not speak for the activity of the process.

It is not devoid of interest to compare the detection of CRP with the positive results of the generally accepted laboratory tests. Among the patients with rheumatism in the active phase CRP was revealed in 81%, accelerated ESR - in 57%, positive Waldman test - in 54%, monocytosis - in 38%, leukocytosis - in 33%, microhematuria - in 29%, positive formal reaction - in 24%, and a positive Bittorf-Tushinskiy test - 10% of the cases. The resulting data testifies to the expressed advantage of the CRP test compared to the generally accepted laboratory tests for rheumatism.

Conclusions

The results of studying the CRP test on 895 patients with various nosological forms show that this pathological protein appears in the blood

during diseases which have as their basis an inflammatory or necrobiotic process. The content of CRP depends on the acuteness and latitude of the pathological process. Setting up the test in the earliest periods from the day of development of the disease makes it possible to determine CRP more frequently and in a greater quantity. As the activity of the process abates the concentration decreases and the number of positive CRP tests is lowered.

The disappearance of CRP from the blood (especially against a background of hormone therapy) does not always testify to the liquidation of the pathological process. Only after a comparison of the clinical picture of the disease with other laboratory tests and a repeatedly negative CRP test is it possible to resolve the question of remission. The CRP test is of very great help in the differential diagnosis between prolonged stenocardia and myocardial infarction, the active phase of rheumatism and the non-active, expressed polyarthralgia and subclinical aggravation of infectious arthritis.

The evaluation of such a test should be based on the clinical picture of the main disease, taking into consideration foci of chronic infection, during which CRP may be determined in insignificant concentrations.

Test for C-reactive protein in healthy persons and patients with foci of chronic infection, certain diseases of the circulatory organs and collagen diseases

Group investigated		Number investigated	Test for C-reactive protein					
			strongly positive	positive		slightly positive		negative
			4 mm and more	3 mm	2 mm	1 mm	traces	
Healthy		77	--	--	--	--	--	77
Foci of chronic infection	Periodontitis	3	--	--	--	--	2	1
	Tonsillitis	85	--	--	--	5	24	56
	Highmorit's	4	--	--	2	1	1	--
Neurocirculatory dystonia		23	--	--	--	--	--	23
Atherosclerosis of coronary vessels	Stenocardia	82	--	--	--	4	6	72
	Myocardial infarction	87	31	19	25	5	5	2
Congenital heart defects		5	--	--	--	--	--	5
Protracted septic endocarditis		47	12	8	13	5	3	6
Collagen diseases	Erythematous chronio-sepsis	8	--	--	3	5	--	--
	Nodular periarteritis	3	1	1	1	--	--	--
	Rheumatoid polyarthritis	132	20	25	30	25	6	26
	Rheumatism, Active phase, Joint-cardiac form	48	26	11	5	2	3	1
	Rheumatism, Active phase, Cardiac form	258	29	20	61	60	31	57
	Rheumatism, Inactive phase	110	--	--	--	5	10	95
Total		972	119	84	140	117	91	421